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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,396	DOBIE, KENNETH W.	
	Examiner	Art Unit	
	James D. Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 11 is drawn to a compound 8 to 50 nucleotides in length that specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding CD36L1.

The specification as filed contains only a definition of the term "active sites"; it does not provide a description of the actual active sites that might be targeted by the invention of the instant application. Additionally, the specification only provides that such sites are experimentally determined; no further identification of sequences encoding any active sites has been described that might lead one of skill in the art to recognize that applicants were in possession of the claimed entities at the time of filing. Such a claim thus amounts to an invitation to experimentation. Since applicant has not described such characteristics, the skilled artisan would not have been able to envision what constitutes the specific active sites as claimed in the instant application.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of CD36L1 expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of CD36L1 expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of CD36L1 in human cells or tissues using antisense compounds, or treating animals having a condition which may be cardiovascular disease, altered lipid metabolism, a metabolic disorder, or atherosclerosis associated with, CD36L1 comprising administering to animals antisense compounds so that expression of CD36L1 is inhibited. The specification teaches antisense-mediated inhibition of CD36L1 *in vitro*.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene

inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) article by Braasch et al. opens by emphasizing that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal

structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379.

Braasch et al. discusses the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for

rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Further, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of CD36L1 expression *in vitro* as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases suspected of being associated with CD36L1 expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed

fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Said claims are drawn very broadly to compounds and methods of treating or preventing any condition or disease suspected of being associated with CD36L1 expression in humans or animals. The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and /or tissues harboring CD36L1 expression such that all harmful expression is inhibited, that healthy expression is appropriately permitted *in vivo,* and further, that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with CD36L1 expression *in vivo*. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with CD36L1 expression in humans, or their tissues or cells, and since determination of these factors for a particular target gene in an organism is highly unpredictable, one of ordinary skill in the art would be unable to practice the invention as presented in the specification over the scope claimed.

Furthermore, the instant specification fails to provide one of skill in the art guidance for the selection of pharmaceutical oligo compounds without engaging in undue trial and error experimentation since it is clear from the references above that in vitro and cellular screening do not correlate with pharmaceutical oligo compounds that function in an *in vivo* environment. The

specification in general fails to provide adequate guidance to overcome the obstacles and unpredictability of oligo therapy that are exemplified in the references above.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Acton et al. The above claims of the instant application are drawn to antisense compounds that target and inhibit the expression of CD36L1.

Acton et al. teach antisense compounds that target and inhibit the expression of CD36L1 (claims 1, 4, 5, and abstract, col. 18-22).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Acton et al. (U.S. Patent Number 5,965,790), in view Calvo et al. and Baracchini et al. (U.S. Patent Number 5,801,154).

The claims are drawn to antisense compounds 8-50 nucleobases in length that target and inhibit the expression of CD36L1, and to internucleoside, sugar, or nucleobase modifications and chimeras of said antisense compounds, and compositions providing for their *in vivo* use.

Acton et al. teach isolated nucleic acids that target CD36L1 (SR-B1 of Acton et al.) and modify its expression. Acton et al. does not teach compositions comprising internucleoside, sugar, nucleobase, and 2' modifications, chimeras, and compositions providing for their *in vivo* use.

Calvo et al. teach the cDNA sequence encoding CD36L1.

Baracchini et al. teaches modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, and chimeras.

It would have been obvious to one of ordinary skill in the art to make antisense oligos to inhibit CD36L1, because antisense inhibition of said protein had been previously taught by Acton et al., and since the sequence had been previously taught by Calvo et al. It also would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini et al. into either the antisense compounds of Acton et al., or into those designed from the complementary sequence of CD36L1 as taught by Calvo et al., because Baracchini et al. teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation. One would have been motivated to create such compounds because Acton et al. teach that inhibiting CD36L1 may counteract cardiovascular disease,

aberrent lipid metabolism, metabolic disorders, or atherosclerosis, and since Baracchini et al. teach that introducing modifications to said compounds would prolong the activity of such antisense compounds. Finally, one would have a reasonable expectation of success given that antisense-mediated inhibition of CD36L1 was previously described by Acton et al., and since modifications to enhance the activity of antisense compounds as taught by Baracchini et al. are routinely performed by one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

*** James D. Schultz
June 3, 2002

ANDREW WANG
PRIMARY EXAMINER